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PATENT
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RESPONSE UNDER 37 C.F.R. § 1.116
EXPEDITED PROCEDURE EXAMINING GROUP 1637

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:

Richard W. Tseng & Michael K. Samoszuk

Serial No.: 09/747,165

Title: BCR-ABL GENE REARRANGEMENT ASSAY METHOD

Filing Date: December 22, 2000

Group Art Unit: 1637

Examiner: Jeffrey Norman Fredman

CERTIFICATE OF MAILING

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RESPONSE TO OFFICE ACTION

Commissioner for Patents
Washington, DC 20231
Box After Final

Sir:

In response to the Office Action mailed on August 7, 2002 ("Paper No. 14"), please consider the following remarks.

The present invention relates in part to assay methods for specifically detecting and/or quantifying bcr-abl gene rearrangements. In particular, the presently claimed methods can provide highly reproducible qualitative and quantitative results in which the presence and/or amount of three different bcr-abl translocations may be determined in a single assay.

Claims 1-13 are presently pending in the instant application. Applicants respectfully request reconsideration of the claimed invention in view of the foregoing amendments and the following remarks.

Non Art-Related Remarks

35 U.S.C § 112, Second Paragraph

Applicants respectfully traverse the rejection of claims 2 and 3 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the present invention.

When determining definiteness, the proper standard to be applied is "whether one skilled in the art would understand the bounds of the claim when read in the light of the specification." *Credle v. Bond*, 30 USPQ2d 1911, 1919 (Fed.Cir.1994). See also *Miles Laboratories, Inc. v. Shandon, Inc.*, 27 USPQ2d 1123, 1127 (Fed.Cir.1993) ("If the claims read in the light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more.").

"Real Time PCR"

Applicants respectfully disagree with the Examiner's assertion that the phrase "real time PCR" in claims 2 and 3 is allegedly indefinite as "all PCR amplification reactions are conducted in real, as opposed to imaginary time." Paper No. 14, page 2. It is respectfully submitted that the Examiner's interpretation of the phrase remains completely uninformed by the understanding of this phrase within the relevant art. *See, e.g.*, MPEP §2173.02 ("Definiteness of claim language must be analyzed, not in a vacuum, but in light of... [t]he teachings of the prior art; and [t]he

claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made").

As Applicants noted in their previous response, the phrase "real time PCR" is well known to those of skill in the art as referring to specific PCR methods in which a signal emitted from the assay is monitored during the reaction as an indicator of amplicon production during each PCR amplification cycle (*i.e.*, in "real time"), as opposed to conventional PCR methods, in which an assay signal is detected at the endpoint of the PCR reaction. As an indication of the acceptance of this term by those of skill in the art, Applicants provided the partial results of a search of the *Medline* database, which revealed 383 publications in which the term is used in the title.

In the present office action, the Examiner agrees that numerous publications by artisans (213 according to the Examiner's search) use the phrase "real time PCR" in the publication's title.[1] Paper No. 14, page 11. Rather than acknowledging that this common usage indicates that those of skill in the art clearly understand the metes and bounds of the phrase, the Examiner instead argues that "these papers do not use the term to mean the same thing," and refers in particular to the protocols and instruments disclosed in two of the publications. *Id.* Applicants respectfully submit, however, that whether or not different protocols and instruments are used in performing real time PCR is irrelevant to whether or not the skilled artisan is reasonably informed of the metes and bounds of claims using the phrase "real time PCR." Just as the skilled artisan understands the meaning of the term "PCR" regardless of the particular protocol employed, the two new publications to which the Examiner refers indicate that the skilled artisan clearly understands the phrase "real time PCR" regardless of the particular protocol employed.

For example, the Dehée *et al.* publication cited by the Examiner discloses the use of the commercially available "Taqman" system in real time PCR, and describes real time PCR as follows: "during each PCR cycle one molecule of reporter dye is cleaved for each target molecule

[1] The Examiner first noted that the partial search results were not attached to Applicants' previous response. Paper No. 14, page 11. Applicants respectfully submit that if papers became separated from Applicant's response, it was due to an error at the Patent and Trademark Office. Should such an event occur again, the Examiner is invited to contact the undersigned for replacement of the pages.

amplified. The released reporter fluorescence is measured in real time." Dehée *et al.*, page 39, right column, last paragraph. Similarly, the Aldea *et al.* publication cited by the Examiner uses a different commercially available system, referred to as "LightCycler," for precisely the same purpose. For the convenience of the Examiner, a description of the LightCycler system is attached hereto as Appendix A. As noted on page 3, first paragraph, "[t]he LightCycler offers kinetic quantification, a fast, accurate way for quantification by PCR. Real-time, kinetic quantification allows measurements to be made during the log-linear phase of a PCR... [as opposed to methods in which] data were acquired only in the plateau phase of the PCR (end-point determination)"

Thus, the each of the publications cited by the Examiner clearly confirm that the phrase "real time PCR" as used in the art refers to a PCR method in which a signal emitted from the assay is monitored during the reaction as an indicator of amplicon production during each PCR amplification cycle, as opposed to conventional PCR methods, in which an assay signal is detected at the endpoint of the PCR reaction. The fact that the authors of the publications cited by the Examiner use different protocols and instruments, but still recognize that each is using "real time PCR," supports the conclusion that the skilled artisan is reasonably informed of the metes and bounds of the phrase "real time PCR."

Applicants respectfully submit that, from the point of view of the skilled artisan, the assertion that the phrase "real time PCR" is allegedly indefinite because "all PCR amplification reactions are conducted in real, as opposed to imaginary time" (Paper No. 14, page 2) is an interpretation of the phrase that is uninformed by the knowledge available to those of skill in the art. Moreover, Applicants respectfully submit that a patentee is free to be his or her own lexicographer in providing a meaning to a phrase, so long as that meaning is made clear in the specification or file history. *See*, MPEP § 2173.05(a). Applicants have clearly indicated the meaning of the phrase "real time PCR" for purposes of the present application.

Applicants respectfully submit that, because of its common usage by those of ordinary skill in the art, the skilled artisan is reasonably apprised of the scope of the present claims with

regard to the phrase "real time PCR." 35 U.S.C. §112, second paragraph, demands no more. Therefore, because the claims, when properly interpreted, meet the standards of 35 U.S.C. §112, second paragraph, Applicants respectfully request that the rejection be reconsidered and withdrawn.

Art-Related Remarks

35 U.S.C. § 103

Applicants respectfully traverse the rejection of claims 1-6 and 8-13 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Mensink *et al.*, *British J. Haematol.* 102: 768-774 (1998) in view of Hariharan *et al.*, *EMBO J.* 6: 115-119 (1978) and further in view of Shtivelman, *Cell* 47: 277-284 (1986).

To establish a *prima facie* case of obviousness, three criteria must be met: there must be some motivation or suggestion, either in the cited references or in knowledge available to the ordinarily skilled artisan, to modify or combine the references; there must be a reasonable expectation of success in combining the references; and the references must teach or suggest all of the claim limitations. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991) *See also,* MPEP §2143.

As Applicants noted in their previous response, the instant invention can provide highly reproducible qualitative and quantitative results in which the presence and/or amount of three different bcr-abl translocations may be determined in a single assay by using the eight specifically designed primers and probes recited in the claims. Such an assay is often referred to as a "multiplex" assay.

In contrast, the Mensink *et al.* publication discloses a method for quantitation of a bcr-abl cDNA fragment using only one set of primers and one probe for bcr-abl fragment. The primers disclosed in the Mensink *et al.* publication are different from those recited in the present claims. The Hariharan and Shtivelman publications are cited for the alleged disclosure of cDNA sequences for BCR and ABL coding regions, respectively. The Examiner contends that that "the only significant difference between the prior art and the current claims is the particular primers

selected from the BCR and from the ABL sequences" (Paper No. 14, page 12), and that the primers of the claims "simply represent structural homologs" of the primers in the cited publications (id., page 6).

Applicants previously noted that there is nothing, other than the Examiner's bare assertion, to indicate that the primers referred to in the instant claims are "structural homologues" of the primers disclosed in the Mensink *et al.* publication. While the individual nucleotides making up typical nucleic acids are chosen from the same "alphabet" of A, T, G, and C, the relative arrangement of nucleotides provides unique structural and functional properties to any particular nucleic acid that are not "homologous" to other nucleic acids having a different arrangement of nucleotides.

In response to Applicant's arguments in this regard, the Examiner alleges that "[a]n ordinary practitioner would expect successful detection of the BCR-ABL translocation from every primer selected according to the methodology taught by Eder," which allegedly "teaches computer software to select primers in the BCR and ABL genes." Paper No. 14, page 12. Applicants note that the Eder *et al.* publication is not of record in this rejection, and thus request clarification of the status of this rejection.

More importantly, Applicants respectfully submit that the Examiner's allegation of the "expectations" of the ordinary practitioner is unsupported by any evidence of record, and is, in fact, contrary to the understanding of those skilled in the art. Rather, the skilled artisan is well aware that each potential primer in a given nucleic acid sequence is <u>not</u> structurally or functionally equivalent. For example, He *et al.*, *BioTechniques* 17: 82-87 (1994) notes that primers that differ even "slightly" in position can exhibit 100- to 1000-fold differences in amplification sensitivity, and that "a trial-and-error" approach must be used to identify useful primers. He *et al.*, abstract. An excerpt from Robertson and Walsh-Weller, *Meth. Mol. Biol.* 98: 121-126 (1998) confirms that, simply because a computer program is used to select sets of primers, the skilled artisan would not expect every primer set to be either structurally or functionally homologous. *See, e.g.*, Robertson and Walsh-Weller, pages 122-123 (while "there are guidelines, as reported by numerous authors, that may be useful in designing effective

primers... [d]espite a gallant attempt at optimization of the PCR and primer design, poor sensitivity might only be relieved when new primer pairs are tried") (citing He *et al.*).

Furthermore, the Robertson and Walsh-Weller publication also cautions on page 124 that the results obtained from primer design software, such as that allegedly disclosed by the Eder *et al.* publication, must be "regard[ed]... with healthy skepticism." Current software algorithms suffer from the fact that "important factors which influence the stability of nucleic acids have yet to be identified." Kämpke et al., Bioinformatics 17: 214-25 (2001), page 224, right column. This is particularly true in multiplex PCR assays, such as those of the instant claims. See, e.g., *id.*, page 214, right column ("The design complexity increases in so-called multiplex PCR.... [T]his requires that physical parameters such as cycle number, cycle duration and annealing temperature are identical for all of the PCR reactions. Moreover, the analysis of unintended primer-primer interactions becomes more intricate"). As a result, "a trial-and-error" approach continues to be required to obtain useful primers, particularly for multiplex primer sets.

Applicants respectfully submit that, when properly considered, it is apparent that an "ordinary practitioner" would clearly not expect successful detection of the BCR-ABL translocation from every primer selected from a particular sequence. Applicants, therefore, request that the Examiner cite objective evidence in support of the allegation to the contrary. It is equally apparent that an "ordinary practitioner" would not consider the primers referred to in the instant claims, which can provide highly reproducible qualitative and quantitative results in which the presence and/or amount of three different bcr-abl translocations, "structural homologues" of the primers disclosed in the Mensink *et al.* publication.

To provide a *prima facie* case of obviousness, there must be some motivation, either provided by the cited publications themselves or in the knowledge generally available in the art, to arrive at the specific combination of elements recited in the present claims. *See, In re Dance*, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (there must be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by applicant); *see also, In re Kotzab*, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) ("particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these

components for combination in the manner claimed" in order to support an obviousness rejection) (emphasis added). The fact that "[t]he prior art teaches the same entire structure from which the primers were derived" (Paper No. 14, page 13) provides no reasoning as to why the skilled artisan would have arrived at the specific sequences referred to in the instant claims. Applicants respectfully submit, therefore, that no *prima facie* case of obviousness has been established.

Moreover, even if the Examiner is correct that a *prima facie* case of obviousness has been established, such a *prima facie* case may be rebutted by evidence of superior results. *See, e.g.*, MPEP §2144.09. As noted previously, the instant claims provide methods by which the presence and/or amount of three different bcr-abl translocations may be determined in a single assay. In contrast, of the publications cited by the Examiner, only one (the Mensink *et al.* publication) detects any bcr-abl translocations are detected, and the methods disclosed in that publication can detect only a single translocation.

In response to this argument, the Examiner asserts that "applicant's statement is not evidence and the specification lacks comparative data," and that these arguments are simply the "arguments of counsel." Paper No. 14, page 12. Applicants respectfully disagree with this characterization. The instant specification describes in detail the claimed methods "designed to be able to amplify and detect all three translocations of the bcr-abl gene, namely e1a1, ba2a2, and b3a2, without interfering with each other and providing highly reproducible results." Specification, page 15, first paragraph. The comparative data of record is provided by the specification, together with the fact that no publications of record provide any such assays. The Examiner must consider comparative data in the specification. *See, e.g.*, MPEP § 716.01(a). Furthermore, while the Examiner contends that "use of the cited prior art method itself in separate experiments might yield equally effective data" (Paper No. 14, page 12), Applicants are not required to compare the claimed invention with subject matter that does not exist in the prior art. *See, e.g.*, MPEP § 716.02(e).

Therefore, because no *prima facie* case of obviousness has been established, or, in the alternative, any *prima facie* case of obviousness may have been established has been rebutted,

Applicants respectfully request that the rejection under 35 U.S.C. §103 be reconsidered and withdrawn.

Likewise, Applicants respectfully traverse the rejection of claims 1-13 as allegedly being unpatentable over Eder *et al.*, *Leukemia* 3: 1383-89 (1999) in view of Hariharan *et al.* and Shtivelman, and in further view of Ercolani *et al.*, *J. Biol. Chem.* 263: 15335-15341 (1988).

It is respectfully submitted that the primers disclosed in the Eder *et al.* publication, like those discussed above from the Mensink *et al.* publication, are different from those recited in the present claims. The Examiner's rejection is predicated upon the flawed conclusion that "the claimed primers simply represent structural homologues, which are derived from sequences suggested by the prior art as useful for primers and probes."

As discussed above, Applicants respectfully submit that, when properly considered, an "ordinary practitioner" would clearly not expect successful detection of the BCR-ABL translocation from every primer selected from a particular sequence, and request that the Examiner cite objective evidence in support of the allegation to the contrary. Applicants also respectfully submit an "ordinary practitioner" would not consider the primers referred to in the instant claims, which can provide highly reproducible qualitative and quantitative results in which the presence and/or amount of three different bcr-abl translocations, "structural homologues" of the primers disclosed in the Eder *et al.* publication, which cannot provide such results.

Moreover, as above, even if the Examiner is correct that a *prima facie* case of obviousness has been established, such a *prima facie* case is rebutted by the superior results provided by the presently claimed methods. Applicants note that the instant claims provide methods by which the presence and/or amount of three different bcr-abl translocations may be determined in a single assay. In contrast, of the publications cited by the Examiner in this rejection, only one (the Eder *et al.* publication) detects any bcr-abl translocations, and the methods disclosed in that publication can detect only two translocations.

Therefore, because no *prima facie* case of obviousness has been established, or, in the alternative, any *prima facie* case of obviousness may have been established has been rebutted, Applicants respectfully request that the rejection under 35 U.S.C. §103 be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully submit that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the address and telephone number listed below so that they may be resolved without the need for additional action and response thereto.

Respectfully submitted,

Date: November 7, 2002

By _____
For Richard J. Warburg,
Michael Whittaker
Registration No. 46,230

FOLEY & LARDNER
P.O. Box 80278
San Diego, CA 92138
Telephone: 858-847-6721
Facsimile: 858-792-6773